

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 January 2002 (03.01.2002)

PCT

(10) International Publication Number
WO 02/00627 A1

(51) International Patent Classification⁷: C07D 231/12, A61K 31/415

(74) Agent: AKSOY DANISMANLIK GIDA TEKSTIL ITHALAT IHRACAT TICARET LTD. STL.; 1. Cadde 5/6, Bahcelievler, 06500 Ankara (TR).

(21) International Application Number: PCT/TR01/00025

(22) International Filing Date: 26 June 2001 (26.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2000/01872 26 June 2000 (26.06.2000) TR

(71) Applicant (for all designated States except US): **FAKO ILACLARI A.S.** [TR/TR]; Buyukdere Caddesi No: 205, 4. Levent, 80650 Istanbul (TR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GUNDUZ, A., Halit** [TR/TR]; **FAKO ILACLARI A.S.**, Buyukdere Caddesi No:205, 4. Levent, 80650 Istanbul (TR). **GOKTEPE, Mehmet** [TR/TR]; **FAKO ILACLARI A.S.**, Buyukdere Caddesi No:205, 4. Levent, 80650 Istanbul (TR). **BAHAR, Mehmet** [TR/TR]; **FAKO ILACLARI A.S.**, Buyukdere Caddesi No:205, 4. Levent, 80650 Istanbul (TR).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

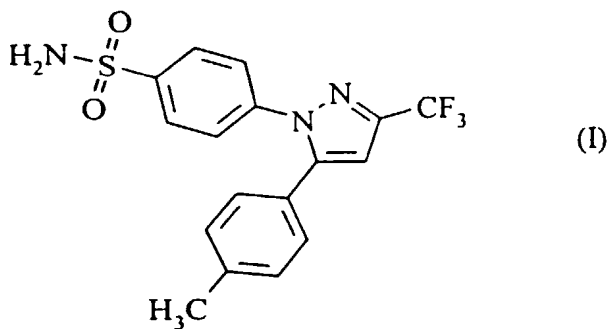
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A CRYSTALLINE FORM OF CELECOXIB

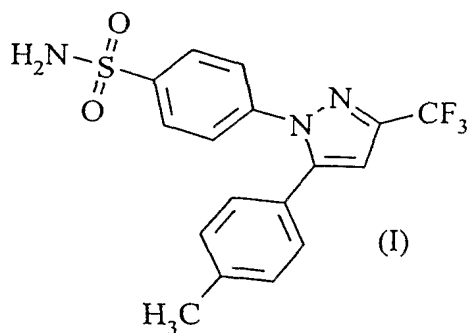


(57) Abstract: A new crystalline form of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide of Formula (I), designated as Form I and a method for its production.

WO 02/00627 A1

A CRYSTALLINE FORM OF CELECOXIB

This invention relates to the pharmaceutical therapeutic agent 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (celecoxib) of formula I



specifically to a new crystalline form of celecoxib with improved properties. This invention further relates to a method for the production of this crystalline form of the agent.

Since prostaglandins play a major role in the inflammation process, the discovery of non-steroidal anti-inflammatory drugs (NSAIDs) has focused on the inhibition of prostaglandin production, especially PGG₂, PGH₂ and PGC₂ production. The use of NSAIDs in the treatment of pain and swelling associated with the inflammation tends to cause side effects by affecting other prostaglandin regulated processes. Thus NSAIDs tend to cause significant side effects including ulcers.

Previous NSAIDs have been found to inhibit some enzymes including cyclooxygenase. Recently, an inducible form of cyclooxygenase associated with inflammation known as cyclooxygenase II (COX-2) or prostaglandin G/M synthase II has been found to exist. This enzyme is more effective in reducing inflammation, causing fewer and less drastic side effects.

Several compounds selectively inhibiting cyclooxygenase II are described in U.S. Patent Nos. 5 380 738, 5 344 991, 5 393 790, 5 466 823, 5 434 178, 5 474 995, 5 510 368, and International Applications WO 96/06840, 96/03388, 96/03387, 95/15316, 94/15932, 94/27980, 95/00501, 94/13635, 94/20480 and 94/26731.

Certain substituted pyrazolylbenzenesulfonamides, specifically celecoxib (4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) as selective COX-2 inhibitor and their preparation have been described in International Application WO 95/15316. In addition, an efficient preparation of 3-haloalkyl-1H-pyrazoles in a one-pot synthesis which is suitable for large-scale process has been described in International Application WO 96/37476.

International Application No. WO 00/32189 discloses specific celecoxib compositions. In this document a number of problems concerning the formulation of this agent, inter alia, its cohesiveness, low bulk density, low compressibility, poor solubility, etc., are described. According to this document, these disadvantages are caused by the crystal structure of celecoxib. Unformulated celecoxib, which has a crystal morphology that tends to form long cohesive needles, typically fuses into a monolith mass upon compression in a tablet die, which leads to problems in blending the agent uniformly. Further, low bulk density causes problems in processing the small quantities required in the formulation of pharmaceutical compositions.

It has now surprisingly been discovered that celecoxib may exist at least in two crystalline forms, hereinafter designated as Form I and Form II, having different properties.

Certain organic compounds can exist in several different crystal forms, which can have different chemical and physical properties, such as density, hardness, flow properties, etc. Therefore, new crystal forms of existing compounds are of great interest.

The new crystal form of celecoxib reported herein provides improved properties, making it possible to overcome the problems described in the prior art. Since the new crystal form does not have the disadvantages of the known needle-like crystals, it overcomes the problems disclosed e.g. in WO 00/32189.

The object of the present invention, therefore, is to provide a new crystalline form of celecoxib which avoids the problems produced by the known, needle-like crystalline form.

The solution of this object is provided by the new crystalline form of celecoxib as disclosed herein, which we have called "Form I" of celecoxib, and by the corresponding production method, as also described herein.

Crystalline forms are characterised by means of X-ray powder diffraction patterns. For this purpose a PHILIPS PW 1710 based diffractometer was used and Cu-K α -radiation (λ (Cu-K α_1) = 1.54056 Å; λ (Cu-K α_2) = 1.54439 Å) was applied. X-ray diffraction data are provided in terms of 2θ values and corresponding intensities.

The crystalline form of celecoxib designated as Form I according to the present invention is characterised by at least the X-ray powder diffractogram data given in table I:

TABLE I: X-ray Diffraction data of Form I:

Angle [2θ]	Rel.int [%]
14.800	69.0
16.050	78.9
17.875	63.7
19.615	100.0
21.455	96.6
22.080	68.1
22.385	65.4
23.425	62.5
25.330	64.5
29.355	60.8

In a preferred embodiment of the present invention said crystalline form of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide of Form I is further

characterised by at least the following further X-ray powder diffractogram data given in table II:

TABLE II: Further X-ray Diffraction data of Form I:

Angle [2θ]	Rel.int [%]
10.670	33.4
10.970	34.0
12.985	32.4
13.855	17.5
18.340	40.4
18.685	40.0
20.425	19.1
20.670	19.0
23.185	48.7
24.510	37.8
24.930	34.5
25.730	22.8
26.915	23.1
27.630	31.5
28.185	26.2
29.955	32.7
30.375	9.9
31.405	9.6
34.915	15.7
35.585	10.9
37.895	17.9
44.070	9.4
45.250	14.5

(in addition to the dominant reflexes of table I).

An example of the X-ray diffraction pattern of Form I is shown in Fig. 1.

The alternative disadvantageous, needle-like crystal form (designated herein as Form II) which is provided by the methods described in the prior art differs significantly from Form I according to the present invention.

An example of the X-ray diffraction pattern for the known Form II is shown in fig. 2 and the corresponding data are given in Table III.

TABLE III: X-ray Diffraction data of Form II

Angle [$^{\circ}2\theta$]	Rel.int [%]
11.025	27.5
13.285	5.9
15.115	16.5
16.415	91.4
17.625	3.2
18.265	3.6
19.785	5.6
21.820	100.00
22.440	16.9
23.500	2.7
24.620	3.0
25.460	2.7
27.280	21.0
29.885	15.6
31.580	1.5
32.815	9.0
35.185	7.4
38.205	5.8
38.415	4.2
39.695	2.5
40.740	3.7
41.285	0.8
42.960	2.4
43.810	2.7
44.820	4.5
45.415	5.0
46.300	4.9

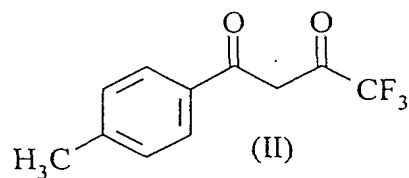
Further, SEM images of the crystallites of Form I according to the invention and Form II obtained by the production methods known in the prior art clearly illustrate the plate like habit of the crystals of Form I in contrast to the needle like habit of the crystals of Form II; as is illustrated by attached Fig. 3 and 4.

One of the main disadvantages of the needle-like crystals of Form II mentioned in WO 00/32189 is their low bulk density. It was found, that the crystals of the invention's Form I are distinctly denser in comparison to the crystals of Form II prepared according to the methods as given in International Applications WO 95/15316 and WO 96/37476. The following densities are typical and characteristic for the crystals of Form I and II, respectively:

	Form I	Form II
bulk density	\geq about 0.270 g/ml	about 0.130 g/ml
tap density	\geq about 0.360 g/ml	about 0.180 g/ml

Consequently, the crystals of Form I are denser than the crystals of Form II, providing improved filtration and drying characteristics. Due to its increased density, better flow properties and lower electrostatic charge, Form I provides further advantages in formulation and capsule preparation.

The present invention further relates to a method for the production of the crystals of Form I of celecoxib by reacting 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione of formula II



with 4-sulphonamidophenylhydrazine hydrochloride in a suitable solvent, crystallizing the resulting 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide from the reaction mixture and recrystallizing it from a suitable solvent.

1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione may be prepared according to Example 2 Step 1 in International Application WO 95/15316.

The preparation of celecoxib, according to the present invention, differs from the production described in WO 95/15316 mainly by the crystallization system used.

Thus, the dione is preferably reacted with 4-sulphonamidophenylhydrazine hydrochloride in isopropanol, instead of absolute ethanol, at reflux temperature. The reaction mixture is treated with activated carbon; after filtering, the product is preferably obtained by crystallizing it by the addition of a non-solvent, especially water (instead of by concentration of the reaction mixture). Finally, the substance is preferably recrystallized from isopropanol and water, instead of methylenechloride/hexane.

Accordingly, the present invention provides further advantages for the preparation of celecoxib by eliminating methylene chloride, a risk for the environment and human health. In addition, it also eliminates the use of n-hexane which causes an ignition and fire risk due to its electrostatic charge accumulation property. Further, according to the present invention, water replaces n-hexane. The use of isopropanol is a further advantage, since it is commercially available and widely used in chemical industry compared to absolute ethanol. Isopropanol should be anhydrous and may be combined with other hydroxylic solvents. Finally, by precipitating the product from the reaction mixture instead of concentrating the reaction mixture to dryness, a higher purity is achieved.

In order to obtain crystals of Form I, celecoxib is most preferably prepared by dissolving celecoxib in a suitable solvent system comprising at least one amide solvent, preferably selected from the group comprising N,N-dimethylformamide, NN-dimethylacetamide and/or mixtures thereof, N,N-dimethylformamide being most preferred, from which solution the crystals of Form I are obtained by the addition of a non-solvent, especially water.

This recrystallization is generally carried out at temperatures of 0 to 80 °C, particularly of 5 to 70 °C, preferably of 10 to 60 °C, more preferably of 15 to 50 °C, most preferably of 20 to 40 °C, e.g., of 25 to 30 °C and/or ambient temperature.

The present invention further includes crystalline celecoxib of Form I crystallography, obtainable by the above described method of production.

Further, the present invention includes pharmaceutical preparations, comprising crystalline celecoxib according to the present invention. Pharmaceutical preparations according to the present invention may be adapted for oral administration and are conveniently presented in the form of, e.g., tablets, capsules, dragees or the like. The formulations may contain ingredients like pharmaceutically acceptable carriers, excipients, adjuvants, etc. as they are known in the art.

Example

Step a: 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione

4'-Methylacetophenone was dissolved in methanol (25 ml) under nitrogen atmosphere. To the stirred solution was added 25% sodium methoxide in methanol (12 ml). The reaction mixture was stirred for 5 minutes and ethyltrifluoroacetate (5.5ml) was added. After refluxing under nitrogen atmosphere for 24 hours the mixture was cooled to room temperature and concentrated. 10 % hydrochloric acid (100 ml) was added. The mixture was extracted with ethyl acetate (4 x 75 ml). The combined organic layer was dried over MgSO₄, filtered and concentrated. The product was obtained as an oily residue.

Step b: 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

1-(4-Methylphenyl)-4,4,4-trifluorobutane-1,3-dione (4.14 g) from step a was stirred in isopropanol (75 ml). 4-sulphonamidophenylhydrazine hydrochloride (4.25 g) was added. The reaction mixture was refluxed under nitrogen atmosphere for 24 hours, cooled to room temperature and filtered, The filtrate was treated with activated carbon at 40–45° C. The product was crystallized by adding water (150 ml). The product was recrystallized from isopropanol and water.

Step c: Isolation of Form I

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (20 g) from step b was dissolved in N,N-dimethylformamide (80 ml) at room temperature. The product was crystallized by addition of water (200 ml). The reaction mixture was stirred for 30 minutes. The product was isolated by filtration, washed with water (3 x 40 ml) and dried. Yield: 18 g.

It corresponded to fig. 3 and showed the X-ray diffraction data presented in fig. 1 and tables I and II.

CLAIMS

1. Crystalline 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, characterised by at least the following X-ray powder diffractogram reflexes:

Angle [°2 θ]	Rel.int [%]
14.800	69.0
16.050	78.9
17.875	63.7
19.615	100.0
21.455	96.6
22.080	68.1
22.385	65.4
23.425	62.5
25.330	64.5
29.355	60.8

2. The crystalline 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide according to claim 1, characterised by at least the following further X-ray powder diffractogram reflexes:

Angle [°2 θ]	Rel.int [%]
10.670	33.4
10.970	34.0
12.985	32.4
13.855	17.5
18.340	40.4
18.685	40.0
20.425	19.1
20.670	19.0
23.185	48.7
24.510	37.8
24.930	34.5
25.730	22.8
26.915	23.1
27.630	31.5
28.185	26.2
29.955	32.7
30.375	9.9
31.405	9.6
34.915	15.7
35.585	10.9
37.895	17.9
44.070	9.4
45.250	14.5

3. Crystalline 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, especially according to claim 1 or 2,
characterised in that it has
a tap density of not less than 0.360 g/ml, and/or
a bulk density of not less than 0.270 g/ml.

4. A method for the production of the crystalline substance according to any one of claims 1 to 3,

characterised in that 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione is reacted with 4-sulphonamidophenylhydrazine hydrochloride in a suitable solvent, the resulting 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is crystallized from the reaction mixture and is recrystallized by solvent precipitation from a suitable solvent.

5. The method according to claim 4,
characterised in that the reaction is carried out in isopropanol.

6. The method according to any one of claims 4 or 5,
characterised in that 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is crystallized from the reaction mixture by the addition of a non-solvent, especially water.

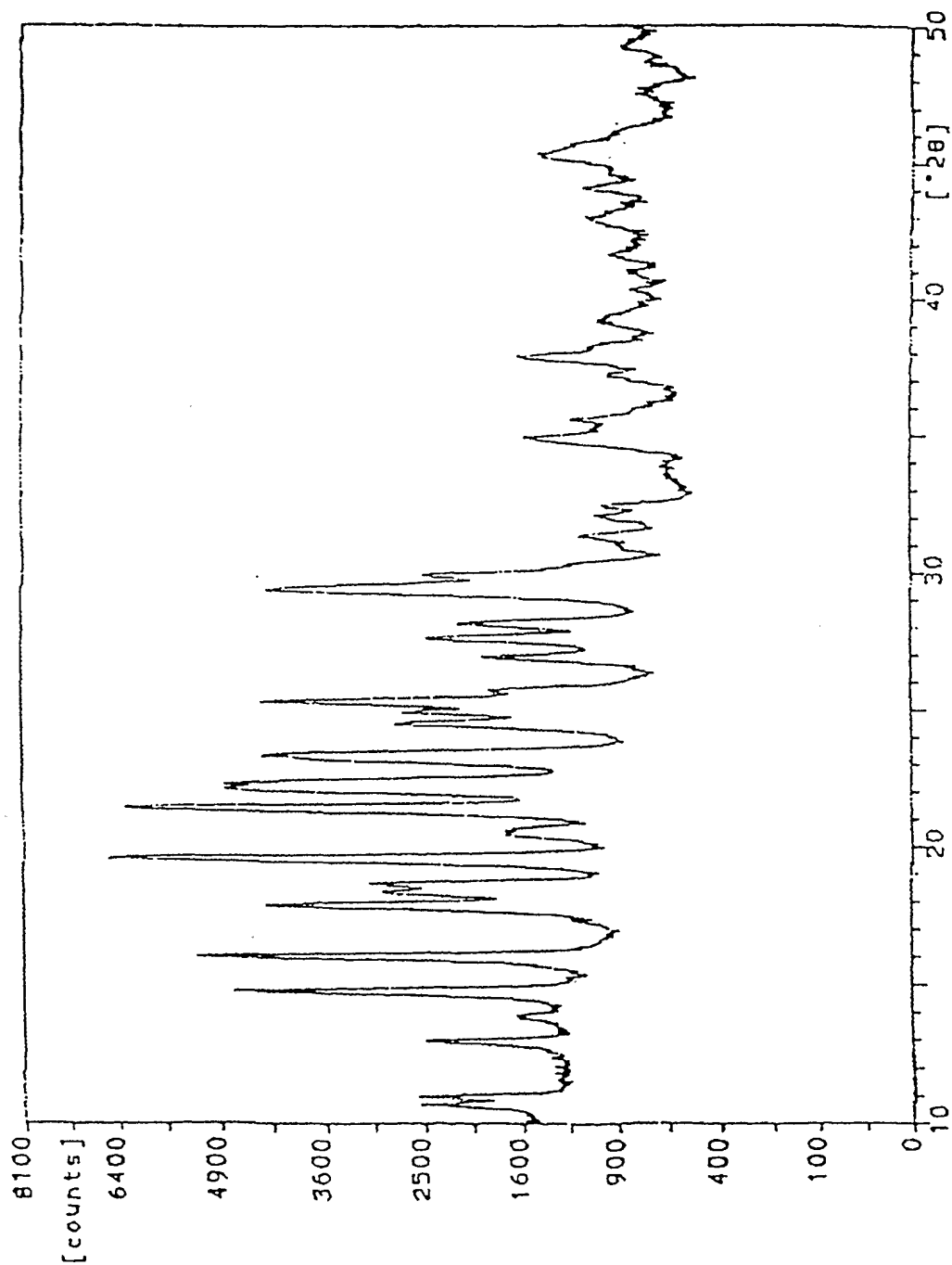
7. The method according to any one of claims 4 to 6,
characterised in that 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is recrystallized from a solvent system comprising at least one amide solvent.

8. The method according to any one of claims 4 to 7,
characterised in that 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is recrystallized from a solvent system comprising at least one amide solvent by addition of a non-solvent, especially water, at a temperature between 0°C and 80°C.

9. The method according to any one of claims 4 to 8, **characterised in that** the amide solvent is selected from the group, comprising N,N-dimethylformamide, N,N-dimethylacetamide and mixtures thereof.
10. Crystalline 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide in accordance with claims 1,2 or 3, obtainable by the method of any one of claims 4 to 8.
11. A pharmaceutical preparation, comprising crystalline 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide in accordance with any one of claims 1,2,3 or 10.

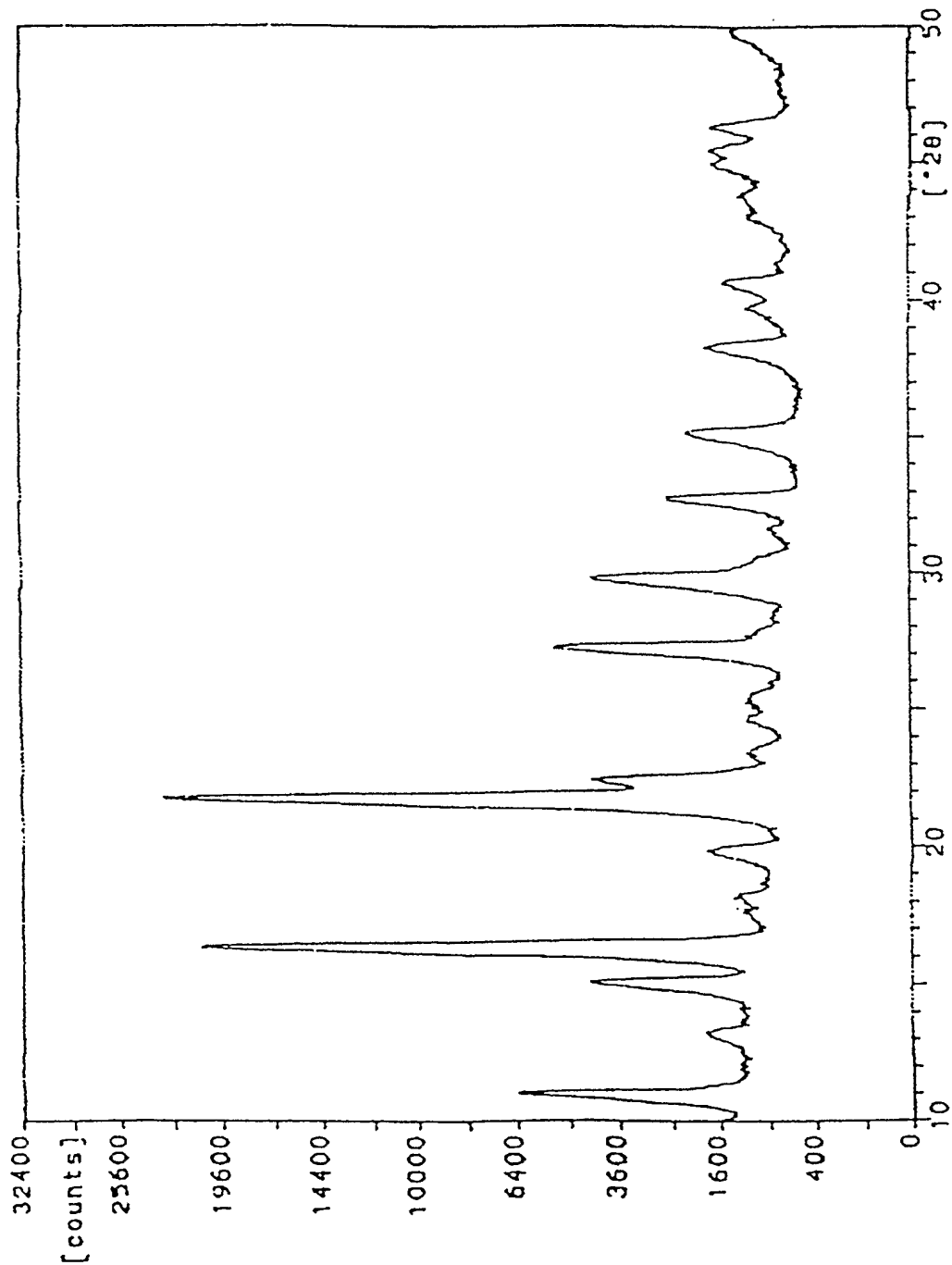
1 / 5

Figure I



2 / 5

Figure 2



3 / 5

Figure 3: SEM image illustrating the plate like habit of the crystals of Form I:

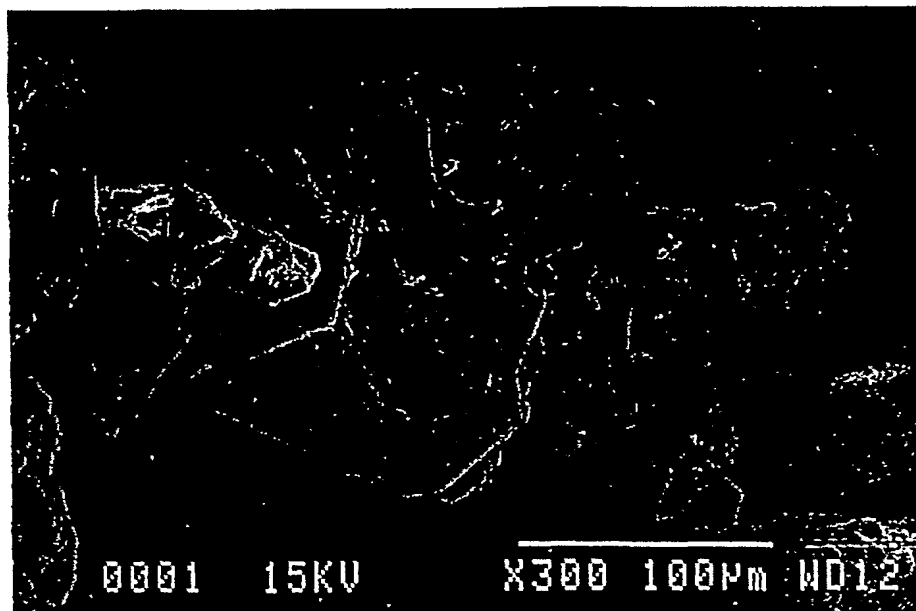


Figure 3

4 / 5

Figure 4: SEM image illustrating the needle like habit of crystals of Form II:

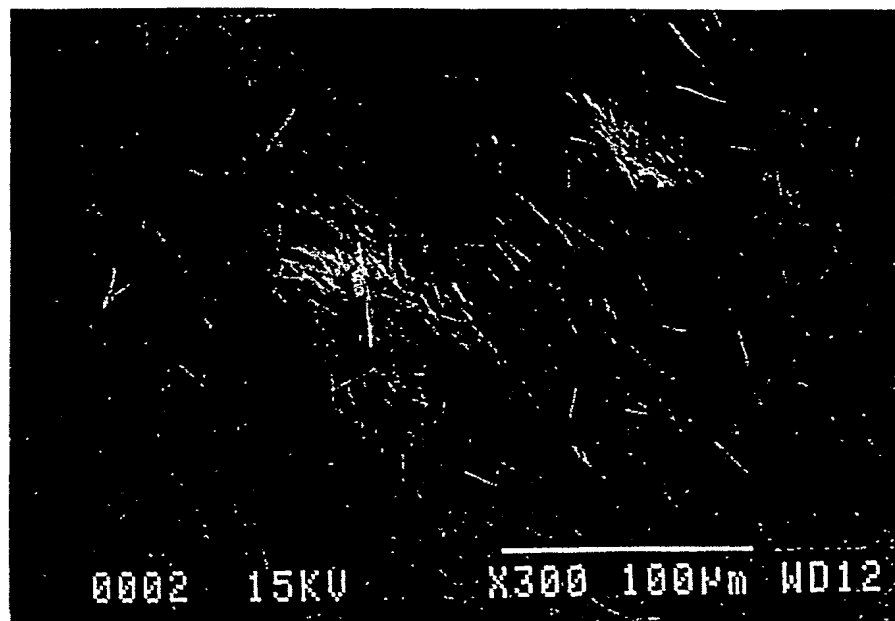
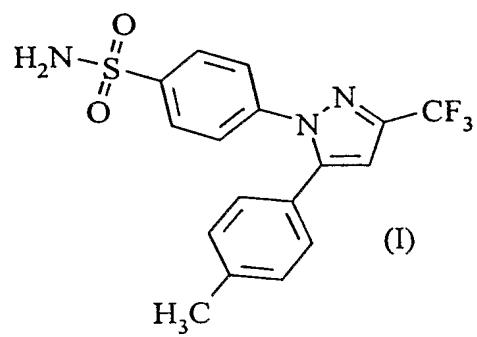


Figure 4

5 / 5

Figure 5



INTERNATIONAL SEARCH REPORT

International Application No

PCT/TR 01/00025

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/12 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 37476 A (SEARLE) 28 November 1996 (1996-11-28) example 1	1-11
X	WO 95 15316 A (GRANETS MATTHEW J ;MIYASHIRO JULIE M (US); SEARLE & CO (US); TALLE) 8 June 1995 (1995-06-08) page 64 -page 65, line 7; example 2 --- -/--	1-11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

26 September 2001

Date of mailing of the international search report

02/10/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

De Jong, B

INTERNATIONAL SEARCH REPORT

Int ional Application No

PCT/TR 01/00025

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PENNING, THOMAS D. ET AL: "Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-'5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-ylbenzenesulfonamide (SC-58635, Celecoxib)" J. MED. CHEM. (1997), 40(9), 1347-1365 , XP002114833 page 1356, left-hand column, line 18 - line 29 ----	1-3,10, 11
P,X	WO 01 42222 A (MIYAKE PATRICIA J ;FERRO LEONARD J (IL); PHARMACIA CORP (US)) 14 June 2001 (2001-06-14) page 4 -page 5; example 2 page 11 -page 14 page 52 -page 57 ----	1-11
P,X	WO 00 42021 A (MERCK FROSST CANADA INC ;TILLYER RICHARD D (CA); DALTON CHAD (CA);) 20 July 2000 (2000-07-20) page 4; claim 7; example 1 -----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/TR 01/00025

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9637476	A	28-11-1996	AU 708964 B2	19-08-1999
			AU 5873696 A	11-12-1996
			BR 9609043 A	23-02-1999
			CA 2222138 A1	28-11-1996
			CN 1190960 A	19-08-1998
			CZ 9703689 A3	18-03-1998
			EP 0828717 A1	18-03-1998
			JP 11505848 T	25-05-1999
			NO 975387 A	17-12-1997
			NZ 308875 A	30-08-1999
			PL 323492 A1	30-03-1998
			WO 9637476 A1	28-11-1996
			US 5910597 A	08-06-1999
			US 5892053 A	06-04-1999
WO 9515316	A	08-06-1995	US 5466823 A	14-11-1995
			US 5521207 A	28-05-1996
			AT 187965 T	15-01-2000
			AU 690609 B2	30-04-1998
			AU 1171495 A	19-06-1995
			BR 1100406 A3	08-02-2000
			CA 2177576 A1	08-06-1995
			CN 1141630 A , B	29-01-1997
			CN 1280125 A	17-01-2001
			CN 1280126 A	17-01-2001
			CZ 9601503 A3	11-12-1996
			DE 69422306 D1	27-01-2000
			DE 69422306 T2	18-05-2000
			DK 731795 T3	15-05-2000
			EP 0731795 A1	18-09-1996
			EP 0924201 A1	23-06-1999
			EP 0922697 A1	16-06-1999
			EP 0923933 A1	23-06-1999
			ES 2141916 T3	01-04-2000
			FI 962249 A	29-05-1996
			GR 3032696 T3	30-06-2000
			HK 1013649 A1	07-07-2000
			HU 74180 A2	28-11-1996
			JP 2000109466 A	18-04-2000
			JP 3025017 B2	27-03-2000
			JP 9506350 T	24-06-1997
			KR 229343 B1	01-11-1999
			KR 263817 B1	16-08-2000
			KR 261669 B1	15-07-2000
			LU 90698 A9	13-02-2001
			NO 962184 A	29-05-1996
			NZ 276885 A	30-08-1999
			PL 314695 A1	16-09-1996
			PT 731795 T	31-05-2000
			RU 2139281 C1	10-10-1999
			WO 9515316 A1	08-06-1995
			US 6156781 A	05-12-2000
			US 5510496 A	23-04-1996
			US 5563165 A	08-10-1996
			US 5508426 A	16-04-1996
			US 5516907 A	14-05-1996
			US 5504215 A	02-04-1996
			US 5753688 A	19-05-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/TR 01/00025

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9515316 A		US 5760068 A	02-06-1998
		ZA 9409418 A	28-11-1995
WO 0142222 A	14-06-2001	WO 0141536 A2	14-06-2001
		WO 0141761 A2	14-06-2001
		WO 0141762 A2	14-06-2001
		WO 0141760 A2	14-06-2001
		WO 0142221 A1	14-06-2001
		WO 0142222 A1	14-06-2001
WO 0042021 A	20-07-2000	AU 3028500 A	01-08-2000
		WO 0042021 A1	20-07-2000
		US 6150534 A	21-11-2000
		US 6232472 B1	15-05-2001